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REPORT NO. 862

ANALYSIS OF LASER INDUCED SKIN BURNS BY A DAMAGE INTEGRAL MODEL

(Interim Report)

by

Arnold S. Brownell, Ph.D.

and

MAJ David K. Hysell, VC

19 March 1970

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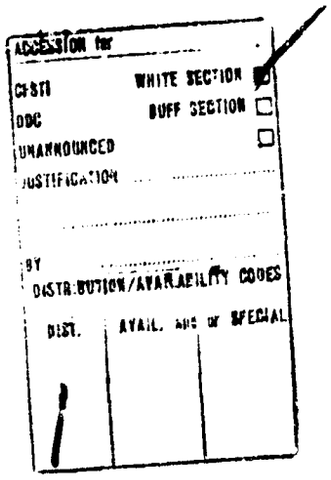

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*Biophysics Division
**Pathology Division
US ARMY MEDICAL RESEARCH LABORATORY
Fort Knox, Kentucky 40121

19 March 1970

Models and Mechanisms of the Effects of Laser Radiation
on Biological Systems
Work Unit No. 010
Biophysics
Task No. 02
Basic Research in Support of Military Medicine
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ABSTRACT

ANALYSIS OF LASER INDUCED SKIN BURNS BY
A DAMAGE INTEGRAL MODEL

OBJECTIVE

To determine the applicability of a proposed mathematical model for thermal injury predictions to experimental data from a study of CO_2 laser radiation induced skin burns.

METHODS

The exposure values for the production of uniform full thickness epithelial burns were used to determine the inactivation rate constants which best fit the data over the exposure time range 0.2 to 5 sec. The appropriate time-temperature values were calculated by heat flow equations based on an assumed isotropic semi-infinite opaque solid.

CONCLUSIONS

The data within the exposure time range of 0.2 to 5 sec are accurately described by the model and can be quantitatively predicted by the equation

$$\Omega = 1.17 \times 10^{64} \int_{t_o}^{t} e^{-49,110/(T_t + 273)}\, dt$$

where T_t is the temperature at time t and Ω is the damage integral with an arbitrarily assigned value of 1.0. For times in excess of 5 sec the values predicted by the model were higher than those determined experimentally.

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ANALYSIS OF LASER INDUCED SKIN BURNS BY A DAMAGE INTEGRAL MODEL

INTRODUCTION

Programs set up to evaluate the potential hazards of lasers involved in military operations have been largely empirical in nature. For a given frequency of radiation, the appropriate combinations of power density and exposure time required to produce some designated level of injury have been determined by trial and error. When the large number of possible combinations of wavelength, power density, exposure time, and the physical, chemical, and biological parameters of target tissue are considered, the need for a more basic approach becomes quite evident. Such an approach would limit, to a reasonable dimension, the number of experiments that are required to define the hazards and safety limits associated with laser use. An understanding of the underlying physical and biological mechanisms involved in injuries induced by laser radiation would permit the extrapolation of data from a limited number of experiments to other appropriate situations.

It is generally conceded that injuries resulting from the use of lasers in military applications will be thermal in nature; that is, they will arise from temperature increases in the exposed tissue resulting from the degradation of the radiant laser energy to thermal energy. The basic principles involved in the analysis of thermally induced injury in cutaneous tissue were defined in a series of papers by Henriques and Moritz. Henriques (1) considered the development of thermal injuries to be time dependent, a rate process that is common to most temperature-sensitive physical or chemical systems. He suggested that by means of a general expression applicable to all rate processes, as used in chemical kinetic theory, a mathematical equation could be developed to predict quantitatively the time-temperature thresholds of tissue injury. By integrating the injury rate process over the time period involved, the contributions from each time increment would be summed to yield the total damage. The proposal has since become known as the damage integral model. In order to calculate accurately the total accrued damage, the precise time-temperature history imposed upon and the thermal sensitivity of the biological system under consideration must be known. Recently published data by Brownell *et al* (2) for CO_2 laser induced porcine cutaneous burns offer the opportunity to apply the idea of the damage integral model to injuries induced by exposure to laser radiation in the time range 0.2 to 20 sec. The model used is essentially that proposed by Henriques (1) and subsequently expanded by Fugitt (3). It is not the intent of this report to define accurately either the time-temperature relations in the tissue or the damage rate function involved, but only to determine the compatibility of the proposed model with the experimental data.

DAMAGE INTEGRAL MODEL

It is assumed that the kinetics of the thermal inactivation of the tissue cells or protein component of the tissue that is used as an indicator of thermal damage can be regarded as a first order reaction at all temperatures under consideration. The rate at which the reaction will proceed can then be given,

$$\frac{dn}{dt} = - k'n \tag{1}$$

where dn is the number of elements inactivated in the time increment dt, k' is the specific reaction rate constant for a given temperature and environmental state and n is the number of elements at any instant.

Upon rearrangement the integral of equation (1) is

$$\int_{n_o}^{n} \frac{dn}{n} = \int_{t_o}^{t} - k'dt \tag{2}$$

or

$$\ln (n/n_o) = \int_{t_o}^{t} - k'dt \tag{3}$$

where n represents the number of active elements remaining at time t and n_o represents the number of elements at time t_o. The specific reaction rate k' can be regarded as a constant only for a given temperature and it will vary as the temperature varies. If equation (2) is integrated over the time interval t_o to t, the resulting equation will yield a numerical value for the surviving fraction for the temperature and time of interest by utilizing the appropriate k'.

During the interval in which a thermal injury is induced by radiation (a type such as is under consideration) the temperature is not constant but varies continually during the episode. Following the onset of exposure, the tissue temperature rises until the end or near the end of the exposure period, subsequently it falls to the initial temperature. Therefore, to complete the mathematical description of the process an expression is needed to relate the inactivation rate constant to temperature.

If the reaction leading to thermal injury is similar to that of many chemical and physical rate processes, the thermal inactivation rate constant should vary with temperature as

$$k' = Ae^{-B/(T + 273)} \tag{4}$$

where A and B are constants. If the reaction meets the necessary thermodynamic criteria, B is equivalent to $\Delta E/R$ where ΔE is the energy of activation and R is the gas constant; the equation becomes equivalent to the integrated form of the Arrhenius equation. In this case A and B will be considered experimentally determinable constants with no special implications.

Combining equations (3) and (4) and rearranging yields

$$\ln (n_o/n) = A \int_{t_o}^{t} e^{-B/(T_t + 273)} \, dt \tag{5}$$

where T_t is the temperature at time t.

It is practically impossible to determine the number of cells or protein molecules inactivated in the skin following a thermal episode. Therefore, an arbitrary level of tissue injury as judged by histological and histochemical techniques must replace the quantitative measure as specified by the expression $\ln (n_o/n)$. Equation (5) then becomes, as suggested by Henriques (1),

$$\Omega = A \int_{t_o}^{t} e^{-B/(T_t + 273)} \, dt \tag{6}$$

where Ω is an arbitrarily chosen level of tissue injury and is designated as the damage integral. Equation (5) allows calculation of the sum of the damage over a specified time interval and temperature. A plot of Henriques' data (1), where he determined the shortest time at which a constant predetermined temperature produced transepidermal necrosis, demonstrates a good fit to equation (5) for conditions under which the temperature at the basal layer of the epidermis could reasonably be assumed to be constant.

In order to use equation (5) to sum the damage accumulated during a thermal episode in which the temperature is varying, it is necessary

to define a function relating temperature to the time of the thermal episode. The opaque semi-infinite model, described by Carslaw and Jaeger (7) and extended by Davis (8, 9) to apply to problems involving radiant heating of tissues, is considered the most appropriate to be used in the calculation of time-temperature relationships at various tissue depths.

OPAQUE SEMI-INFINITE THERMAL MODEL

The data to be analyzed is taken from a study using CO_2 radiation with a wavelength of 10.6 μ as the source of heat. It is assumed that the porcine skin is opaque to radiant energy of this wavelength and the radiation is absorbed at the surface of the skin. The half-layer value of skin and other wet tissue for 10.6 μ radiation is approximately 10^{-3} cm with an absorption coefficient of about 700 reciprocal cm (5, 6).

The following assumptions are pertinent to the opaque semi-infinite model as used: the skin is a semi-infinite isotropic receiver, initially at a uniform temperature throughout; the thermal properties of the skin are constant and do not change with temperature; the surface is perfectly insulated and there are no radiation losses; the radiation input is a square wave, normal to and uniform over the surface of the tissue; heat flow is unidirectional, being perpendicular to the skin surface; and the tissue is opaque to the radiation, which is absorbed at the surface.

Under these conditions, the equations describing the temperature change, as given by Davis (8, 9), are as follows

$$\Delta T(\chi,t) = \frac{.478I}{\sqrt{\mu}}\left[\sqrt{\frac{t}{\pi}}\, e^{-\chi^2/4\alpha t} - \frac{\chi}{\sqrt{4\alpha}}\,\operatorname{erfc}\left(\frac{\chi}{\sqrt{4\alpha t}}\right)\right] \quad 0 \leq t \leq \eta \quad (7)$$

$$\Delta T(\chi,t) = \frac{.478I}{\sqrt{\mu}}\left[\sqrt{\frac{t}{\pi}}\, e^{-\chi^2/4\alpha t} - \frac{\chi}{\sqrt{4\alpha}}\,\operatorname{erfc}\left(\frac{\chi}{\sqrt{4\alpha t}}\right)\right]$$

$$-\left[\sqrt{\frac{t-\eta}{\pi}}\, e^{-\chi^2/4\alpha(t-\eta)} - \frac{\chi}{\sqrt{4\alpha}}\,\operatorname{erfc}\left(\frac{\chi}{\sqrt{4\alpha(t-\eta)}}\right)\right] \quad t > \eta \quad (8)$$

where

I = temperature rise (°C)

η = depth (cm)

t = time (sec)

I = irradiance, absorbed (joules sec^{-1} cm^{-2})

η = exposure time (sec)

μ = thermal inertia, $k\rho c$ (cal^2 cm^{-4} dig^{-2} cm^{-1})

α = thermal diffusivity, $k/\rho c$ (cm^2 sec^{-1})

k = thermal conductivity (cal sec^{-1} cm^{-1} dig^{-1})

c = specific heat capacity (cal gm^{-1} dig^{-1})

ρ = density (gm cm^{-3})

erfc = complementary error function

The temperature change during the exposure period is given by equation (7) and following the termination of radiation exposure by equation (8). The numerical values of the thermal constants used in these calculations, $\mu = 11.8 \times 10^{-4}$ and $\alpha = 8.6 \times 10^{-4}$, were derived experimentally by Davis (8, 9) for porcine skin. A temperature of 36°C was assumed for the temperature at time zero in all cases.

The temperatures, calculated as a function of time, were then used in equation (6) to determine the numerical value of the damage integral for each exposure time. Sixty to 80 equal time intervals were summed over the time during which the damage rate was greater than 1/100 of the maximum damage rate for each case. Damage integrals were determined only for those cases where the exposure time was less than 10 sec. It was thought that the dermal capillary bed may act as a heat sink for longer periods of time, thereby invalidating the assumption of the semi-infinite isotropic feature of the thermal model. Constants A and B in equation (6) were varied to give the closest fit to a damage integral for all cases within the exposure time range of .2 to 10 sec.

RESULTS AND DISCUSSION

The data obtained from the gross evaluation of 2,288 porcine skin burns induced by exposure to CO_2 laser radiation (2) is presented graphically in Figure 1 (next page). The semilogarithmic plot gives the radiant energy density in joules/cm^2 that produces at least a minimally detectable erythema 50% of the time. This was designated as a 1-2 burn.

Selected biopsies were made in order to establish a relationship between the surface appearance of the burn and the depth of damage as judged histologically and histochemically (3). Of the 1-2 burns examined microscopically, approximately 70% were uniform full thickness epithelial lesions, 7% included dermal damage, and the remainder had

only partial epithelial damage. Although the data suggest that the depth of damage may increase slightly as the power density increases, they were not sufficient to establish this effect. The average thickness of the epithelium was 75 μ.

Based on the biopsies, a 1-2 burn is considered equivalent to a histologically defined uniform full thickness epithelial lesion. Therefore, the data in Figure 1 represent the radiant energy density values with a 50% probability of producing thermal damage to a depth of 0.075 cm in porcine skin. This is designated as the damage level.

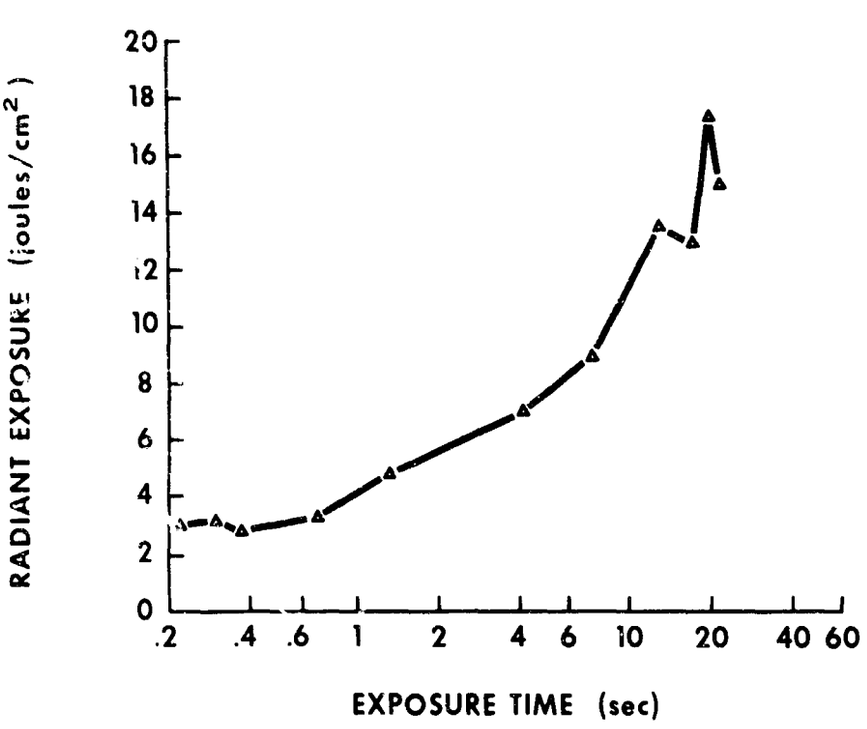

Fig. 1. The incident energy density required to produce visually detectable erythema 50% of the time as a function of the exposure time.

By fixing the thermal constants, α and μ, and arbitrarily assigning a numerical value of 1.0 to the damage integral Ω, it is possible to find the constants A and B for the damage rate function that best fit all the data from .2 to 10 sec exposure time. The following values were found to give a reasonably constant damage integral of 1.0 for nearly all the cases examined:

$$\ln A = 147.518$$

$$B = 49{,}110$$

The total damage integral, as calculated for each exposure time-power density combination is given in column 6, Table 1. With the exception of exposure times .37, .71, and 7.4 sec, the calculated damage integrals are quite close to the assigned value of 1.0.

TABLE 1

Temperature and Damage Integral Values Derived From Experimental Data

Exposure Time (Sec)	Irradiance (watts/cm^2)	Max. Temp. (°C)	Time of Max. Temp. (Sec)	Damage Integral to end of Exposure	Total Damage Integral
.22	13.6	56.2	.230	0.55	1.05
.30	10.6	65.6	.309	0.51	0.98
.37	7.6	60.6	.378	0.08	0.15
	9.0*	65.2	.378	0.50	0.94
.71	4.7	59.6	.717	0.09	0.16
	5.6*	64.1	.717	0.60	0.99
1.3	3.7	63.0	1.306	0.72	1.09
2.3	2.5	61.6	2.306	0.73	1.02
4.1	1.7	60.1	4.11	0.74	0.99
7.4	1.2	59.6	7.40	1.08	1.39

*Adjusted values, see text.

The median radiant exposure values for exposure times .37 and .71 might be considered low relative to those adjacent to them as shown in Figure 1. This could suggest that: (1) for these two exposure times the initial skin temperature of the animals was higher than the other animals, thereby requiring less total energy to raise their skin temperature through the appropriate range and/or (2) errors in dosimetry yielded lower measured values of irradiance than actually were used.

A judgment as to whether these two points are out of line can be made by considering the calculated temperature responses. *A priori*, it can be expected in a system, such as the one considered here, that for a fixed damage response, as the exposure time is decreased, the maximum temperature must increase in order to compensate for the shorter time. A plot of the maximum temperature values versus the exposure time should reveal a smooth, continuous function. The calculated maximum temperature (column 3, Table 1) versus the exposure time is shown in the semilogarithmic plot of Figure 2. It can be seen that all the points cluster closely around a single line with the exception of the two in question. A calculated 18% increase in irradiance values was necessary to give the maximum temperature values for these two points shown in Figure 1 as open circles. Such a difference attributed to dosimetry seems rather high. The adjusted irradiance values were used to recompute these two damage integrals.

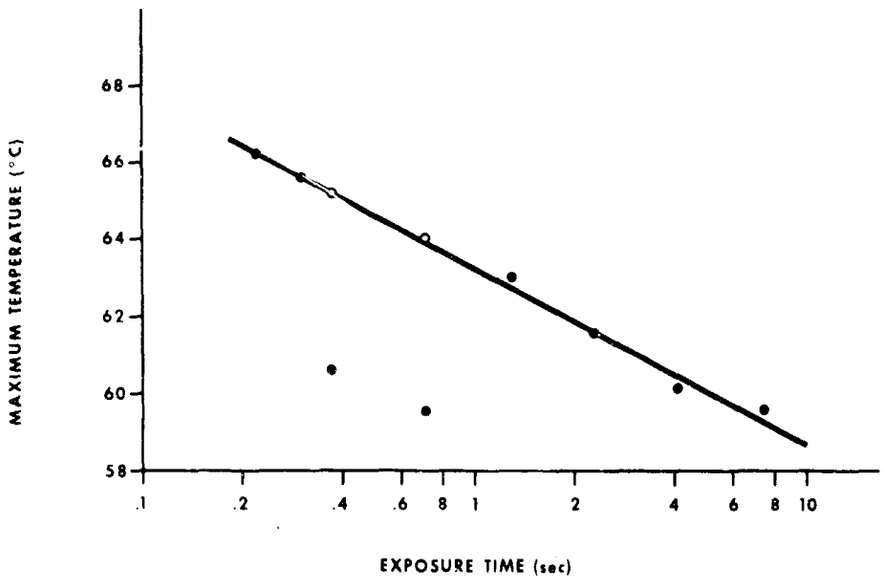

Fig. 2. The calculated maximum temperature attained at the base of the epidermal level as a function of the exposure time to CO_2 laser radiation. The open circles are adjusted values for the exposure times .37 and .71 sec; see text for explanation.

The computed values of the damage integrals are presented graphically in Figure 3. All the values are grouped closely around the line with the exception of that for the longest exposure time. Calculations for longer exposure times indicate that their damage integral values are

even higher. The calculated damage integral values for the exposures of 13 and 20 sec are 24 and 32, respectively. This indicates that the model predicts more severe damage at these longer times than was actually seen. If the dermal capillary bed acts as a heat sink, during long exposures, it could keep the temperature below that predicted by the model. In many cases during long exposure periods, erythema was evident at the site of exposure.

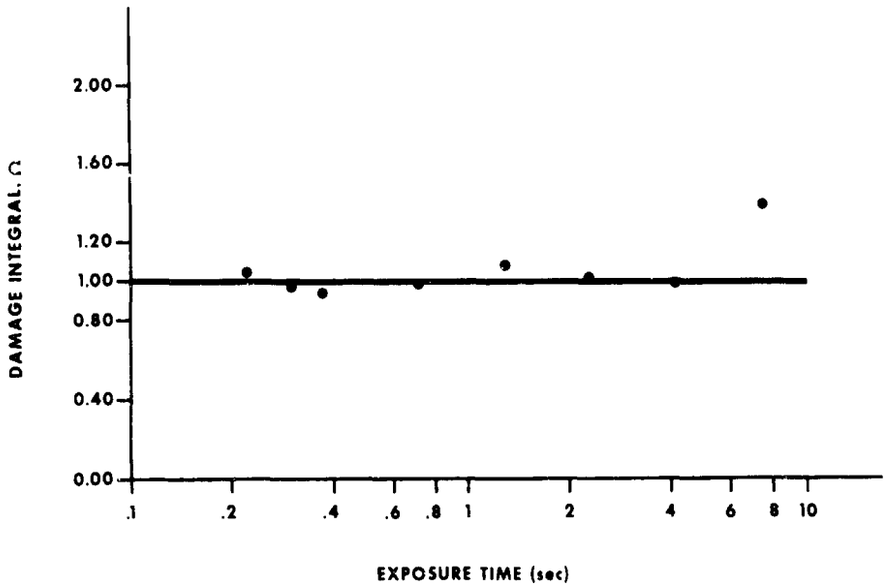

Fig. 3. The calculated damage integral value for uniform full thickness epithelial burns as a function of the exposure time to CO_2 laser radiation.

There are two interesting observations derived from Table 1. As the exposure time is shortened, a greater percentage of the total damage occurs after the exposure is terminated, and the maximum temperature is reached proportionally later following the termination of the exposure. Both of these relations can be influenced by the thermal constants of the tissue under consideration and the depth at which the temperature is calculated.

It should be emphasized that the numerical values derived for the inactivation rate constants are not necessarily the true values. Their derivation is based on the assumption that the heat flow equations used in calculating the temperature response in the tissue accurately describe the real situation. Only accurate inactivation rate constants would be valid for determining threshold levels for other situations where the

energy absorption pattern is different, such as when radiant energy of different wavelengths is used and in pigmented skin.

CONCLUSIONS

An analysis of experimental data defining the threshold values of irradiance as a function of exposure time to CO_2 laser radiation to induce uniform full thickness epithelial burns demonstrated that within the exposure time range of 0.2 to 5 sec the data are accurately described by the damage integral model and can be quantitatively determined by the equation

$$\Omega = 1.17 \times 10^{64} \int_{t_o}^{t} e^{-49,110/(T_t + 273)} \, dt$$

wnere T_t is the temperature at the epidermal-dermal junction at time t during the thermal episode. For times in excess of 5 sec the values predicted by the model were higher than those determined experimentally.

The validity of the time-temperature relations in the epidermis predicted by the opaque semi-infinite thermal model and the thermal constants for porcine skin need to be determined and the model and constants modified if necessary.

Additional experiments to determine damage thresholds at various depths are needed to extend the use of the model in predicting more levels of damage. Such experiments would also permit further evaluation of some of the assumptions inherent in the model.

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13. ABSTRACT

An analysis of experimental data defining the threshold values of irradiance as a function of exposure time to CO_2 laser radiation to induce uniform full thickness epithelial burns demonstrated that within the exposure time range of 0.2 to 5 sec the data are accurately described by the damage integral model and can be quantitatively determined by the equation

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